Case Report

Pulmonary arterio-venous malformations in a patient with a novel mutation in exon 10 of the *ACVRL1* gene

C. Vandenbriele[1,2], K. Peerlinck[1,2], T. de Ravel[3], P. Verhamme[1,2], T. Vanassche[1,2]

[1]Center for Molecular and Vascular Biology, University of Leuven, Belgium, [2]Vascular Medicine and Haemostasis, University Hospitals Leuven, Belgium, [3]Center for Human Genetics, University Hospitals Leuven, Belgium

Mutations of the *ACVRL1* gene are a cause of hereditary haemorrhagic telangiectasia (HHT) type 2. In this case report, we present a patient with isolated pulmonary arterio-venous malformations (PAVMs) without other diagnostic criteria for HHT and a novel mutation in exon 10 of the *ACVRL1 gene*. Other mutations in exon 10 of *ACVRL1* have been linked to the development of pulmonary artery hypertension, but PAVMs are a rare manifestation of HHT associated with *ACVRL1* mutations. A disrupted endothelial TGF-beta/BMP signaling cascade underlies the pathogenesis of HHT, but the exact mechanism of the disease remains unelucidated. In particular, the factors that influence the variable clinical presentation are not fully understood.

Keywords: Rendu-Osler-Weber syndrome, *ACVRL1* gene, Teleangiectasias, Hereditary haemorrhagic telangiectasia, Pulmonary arterio-venous malformations

Introduction

Hereditary haemorrhagic telangiectasia (HHT), or Rendu–Osler–Weber syndrome, is an autosomal dominant multisystemic vascular dysplasia, with an estimated prevalence of around one in 10.000 individuals.[1,2] The clinical manifestations include recurrent epistaxis, muco-cutaneous telangiectasia, gastro-intestinal haemorrhage, and pulmonary, cerebral, and hepatic arterio-venous malformations.[2] Individual patients may present with a wide range of symptoms, and the clinical presentation may vary considerably between affected members of the same family. Because of the variable expression and pleiotropy of HHT, diagnosis can be challenging, particularly in younger individuals, as many of the disease features become more pronounced with age.[3] Therefore, diagnostic criteria have been formulated, with a definitive diagnosis of HHT requiring the presence of three or four of the typical clinical manifestations (epistaxis, telangiectasia, visceral manifestations, and positive family history).[4]

HHT is a genetically heterogeneous disorder. The majority of cases are caused by mutations in either the *ENG* gene on chromosome 9q encoding endoglin (HHT type 1, OMIM 131195), or the *ACVRL1* gene on chromosome 12q encoding the Activin A receptor-like kinase 1 (Alk1, HHT type 2, OMIM 601284).[3,5,6]

Correspondence to: C Vandenbriele, Center for Molecular and Vascular Biology, University of Leuven, Leuven, Belgium. Email: Christophe.Vandenbriele@med.kuleuven.be

Case Report

A 53-year-old woman, with a medical history of short-term memory loss, depression, and migraine, was admitted to the emergency department due to mild exercise-induced shortness of breath. Physical examination revealed a slightly reduced arterial oxygen saturation level, but was further unremarkable. A contrast computed tomography scan of the chest revealed various pulmonary arterio-venous fistula (Fig. 1). Selective pulmonary angiography confirmed these CT findings and the feeding arteries were occluded during this procedure. Gadolinium-enhanced magnetic resonance imaging of the brain — performed due to memory loss — revealed diffuse old ischaemic lesions without obvious cerebral vascular malformations.

As there was no history of epistaxis or gastro-intestinal bleeding, no known family members with HHT, and no telangiectasia of the lips or tongue, the present patient did not meet the full diagnostic criteria for HHT. However, because of the presence of the pulmonary arterio-venous malformations (PAVMs), genetic analysis of the *ENG* gene and the

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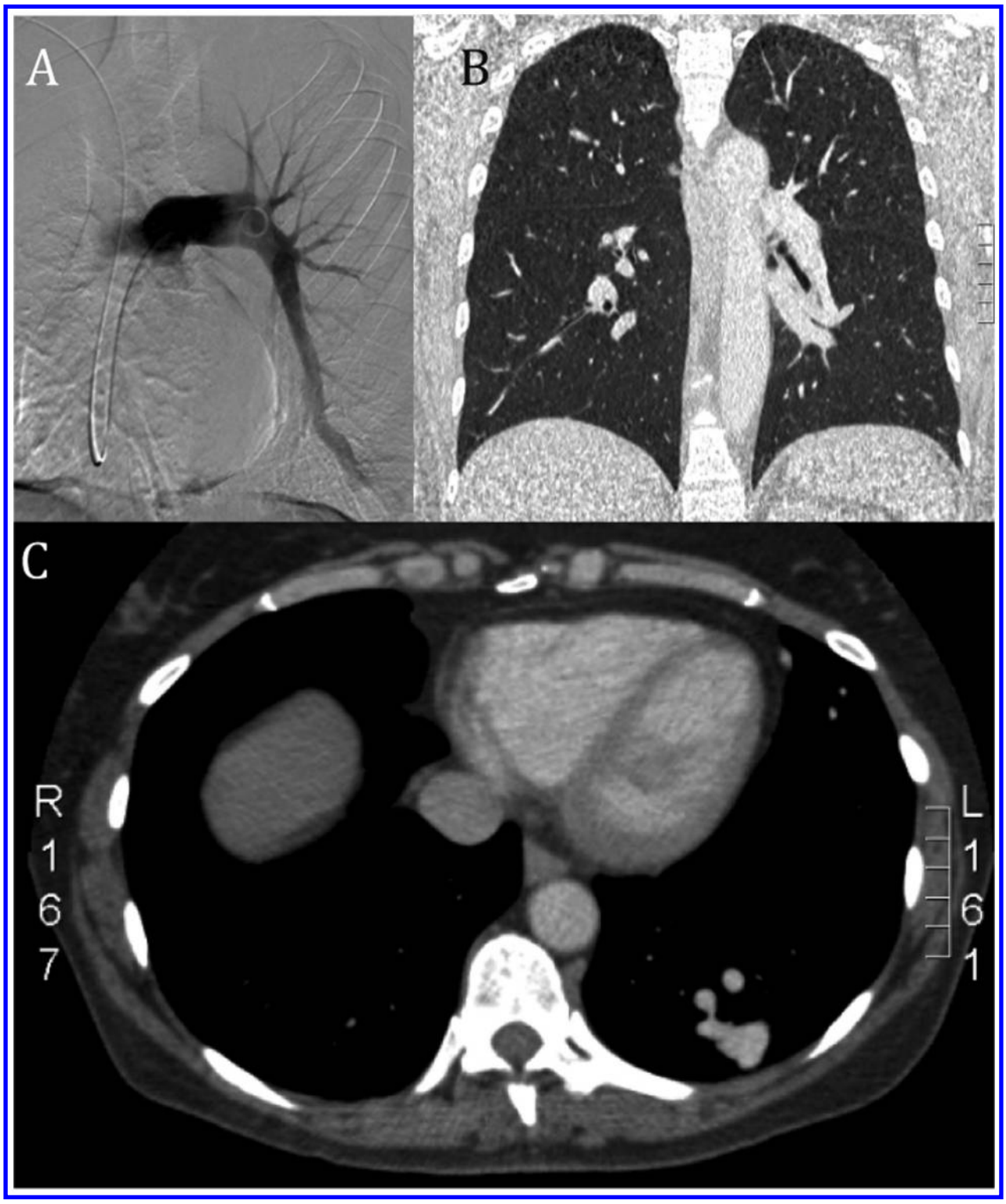

Figure 1 Pulmonary angiography (A) and CT findings (B, C). Axial and coronal contrast-enhanced CT scan (B, C) reveals aneurysmal enlargement and arterio-venous malformation of the left lower lobe pulmonary artery, but no evidence of intraluminal thrombi. These findings were confirmed by contrast-enhanced angiography (A).

ACVRL1 gene was performed, which demonstrated a point mutation in exon 10 of the *ACVRL1* gene (c.1457A>T, p.K486M).

Discussion

We present a 53-year-old patient with PAVMs associated with a novel mutation in exon 10 of the *ACVRL1* gene (c.1457A>T, p.K486M).

Mutations in the gene for the activin receptor-like kinase 1 (ACVRL1), a type I serine-threonine kinase receptor that is involved in the signaling of transforming growth factor beta (TGF-beta) in endothelial cells, are involved in the pathogenesis of HHT type 2. Most mutations associated with HHT are found in exon 3 — coding for the extracellular region — and in exons 7 and 8, which code for the intracellular kinase

domain,[7] whereas mutations in exon 10 account for about 8% of the known mutations.[7]

Although *ACVRL1* mutations interfere with the regulation of angiogenesis,[8] the detailed molecular mechanism by which *ACVRL1* deficiency leads to vascular malformations still remains to be identified.[7]

This patient with pulmonary arterio-venous fistula lacked the typical clinical features of HHT. Although the severity, age of onset, and locations of the vascular lesions are extremely variable from one individual to another, almost 90% of HHT patients have a history of epistaxis, and the vast majority of patients exhibit at least two out of the four criteria.

Moreover, the presence of PAVM is less frequent in HHT type 2, as compared to HHT type 1, which is caused by mutations in the *ENG* gene encoding Endoglin, a co-receptor for TGF-beta.[9]

Although PAVMs frequently remain undiagnosed and asymptomatic, they may — as in this patient — cause hypoxemia and dyspnea due to right-to-left shunting. PAVMs may also result in bleeding complications such as massive haemoptysis or haemothorax, and central nervous system complications such as transient ischaemic attack or stroke due to paradoxical embolism.[10] An increased prevalence of migraine has also been described.[11] This patient was found to have several diffuse ischaemic brain zones, and also suffered from migraine.

Mutations in *ACVRL1*, and especially in exon 10, are known to be associated with the development of pulmonary artery hypertension in HHT type 2 patients.[12] The principal known gene responsible for familial and idiopathic pulmonary arterial hypertension is BMPR2, which encodes the bone morphogenetic protein receptor 2, and is a member of the TGF-beta receptor superfamily. Upon binding of TGF-beta, the formation of a heteromeric receptor complex with *ACVRL1* is required for the activation of the intracellular signaling pathway, ultimately leading to vascular differentiation as well as endothelial proliferation.[13–15]

It remains unclear whether this patient has an atypical and paucisymptomatic presentation of HHT type 2, or whether the phenotype of isolated PAVM is directly linked to the specific mutation described in this report. Previous attempts to find genotype–phenotype correlations in HHT patients have highlighted the variability of the clinical presentation, even between affected members of the same family. Therefore, other genetic and/or environmental factors are likely to influence both the type of vascular malformation and the localization of the affected vasculature. A better understanding of the mechanisms that protect certain vascular regions against the effects of the disrupted TGF-beta signaling may offer valuable clues for future therapeutic strategies.

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